	Beechold/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
Datum Date Date	**CODINGDATE**	Blatt Sheet Feuille	Annule-Nr.: Application No.: 99 945 649.4 Demande n°:
		6	

PRELIMINARY OPINION OF THE OPPOSITION DIVISION

The oppositions are admissible because they meet the requirements of Articles 99 and 100 EPC, as well as Rules 1(1) and 55 EPC.

1. Admissibility of added claims 24-32

The opposition division is of the preliminary opinion that claims 24-32 filed with the letter of 4.2.04 are not admissible under Rule 57a EPC since the objections put forward in regard to claims 1-23 are not overcome by adding further claims.

However, in order to expedite the ongoing opposition proceedings, said claims 24-32 will be regarded as an "auxiliary set of claims" alternative to claims 1-23 as granted (MAIN REQUEST).

2. Added subject-matter

2.1. MAIN REQUEST

The opposition division is of the preliminary opinion that claims 1-23 fulfill the requirements of Article 123(2) EPC.


2.2. AUXILIARY SET OF CLAIMS

Added claims 24-32 as well fulfill the requirements of Article 123(2) EPC.

3. Sufficiency of disclosure

3.1. MAIN REQUEST

OPI has provided experimental data (Annex I - Appendices A-C of letter of 29.4.03) showing that liquid BTX formulations at pH 6 fail to have the alleged stability. Thus, the claimed "invention" appears to be insufficiently disclosed, contrary to Article 83 EPC.

	Beschreibung/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
	Datum Date **CODINGDATE**	Blatt Sheet Feuille 9	Anmelde-Nr.: Application No.: Demande n°: 99 945 649.4

has to remark the following:

None of D1-D26 addresses the same problem as the patent in suit.

The following documents are regarded as being most relevant to the stated problem:

D1 is related to stabilization during the lyophilization procedure.

D12 and D13 disclose a freeze-dried storage stable BTX preparation which comprises an excipient protein providing stability to the toxin complex during dilution and upon lyophilization.

D15 discloses a lyophilized BTX composition with increased stability at higher temperatures.


D18 is a review describing properties and use of botulinum toxin and other neurotoxins referring also to the problem of long-term stability of the toxin and to the factors relevant for the enhancement of stability of neurotoxin solutions as well as to the losses of toxicity on drying.

Other proteins than serum albumin are also mentioned for stabilizing. Moreover, it is stated that drying, "which would have many advantages in long-term stability ... resulted in a substantial loss". Research on the development of a medium and conditions to overcome the losses of drying is being carried out, according to D18.

D19 discloses several considerations in regard to the storage of the toxin:

- "The purpose of human serum albumin is to stabilize the toxin on [a] great dilution" needed for medical use.
- "Best conditions for stability of the toxin in solution are pH 4.2-6.8 and a temperature below 20°C." Although this pH range "diverges from the composition of body fluids, it may be preferred to prevent loss of toxicity and possible formation of a toxoid."
- "Only the crystalline toxin should be used in compounding for medical use."
- "The crystalline toxin is easily inactivated in solution by shaking, which produces bubbles that cause surface denaturation."

Hence, according to D19 the best conditions for stability in solution are pH 4.2-6.8, and at a temperature below 20°C. Solutions can be frozen and stored for years in phosphate buffers at pH 6.2-6.8, or in citrate buffers at pH 5.5. They are also very stable for periods of years in acetate buffer at pH 4.2 even at 20°C but cannot be frozen (p. 45, par. 1).

	Beschreibung/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
	Datum Date Date **CODINGDATE**	Blatt Sheet Feuille 10	Anmelde-Nr.: Application No.: Demande n°: 99 945 649.4

5.2. AUXILIARY SET OF CLAIMS

The remarks directed to claim 1 in regard to inventive step apply *mutatis mutandis* for independent claim 24.

6. Others

Since all parties have requested oral proceedings, a summons is dispatched together with this communication.

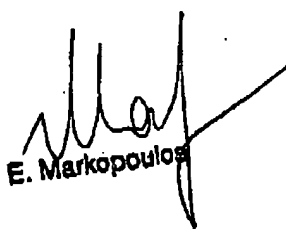
The subject of the oral proceedings will be the grounds of opposition.

In case the parties wish to make further submissions, the final date for doing so will be 2 months before the date of the oral proceedings. New facts and evidence presented after that date need not be considered, unless admitted on the grounds that the subject of the proceedings has changed (Rule 71 (a) EPC).

It should be stressed that the above opinions are merely provisional and non-binding on the opposition division. The points raised are merely those considered to be important serving primarily as a basis for further discussions during the oral proceedings.


B. Paris Antoli


R. Winger


E. Markopoulos